Literature Seminar 2005.7.30 Reiko Wada

Mechanism of Oxidation by Copper-Dioxygen Complex

A large number of biomimetic transition-metal complexes supported by a wide variety of ligands have been developed to evaluate the active site structures and functions of many metalloenzymes.

For copper, a great effort has been made especially in oxygen activation chemistry to provide profound insights into the catalytic mechanisms of copper monooxygenases and copper oxidases.

In today's seminar, Structure and reactivity of Cu/O_2 complex, and the mechanism of oxidation will be discussed.

Reviews : Acc. Chem. Res. 1997, 30, 139-149.
Chem. Rev. 2004, 1013-1045.
Chem. Rev. 2004, 1047-1076.

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   1.1 Role of Cu in biology
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4. Mechanistic Studies.
5. First structural characterization of end-on Cu/O_2 (1/1) complex in enzymes.

1 Introduction.

1.1 Role of Cu in Biology.

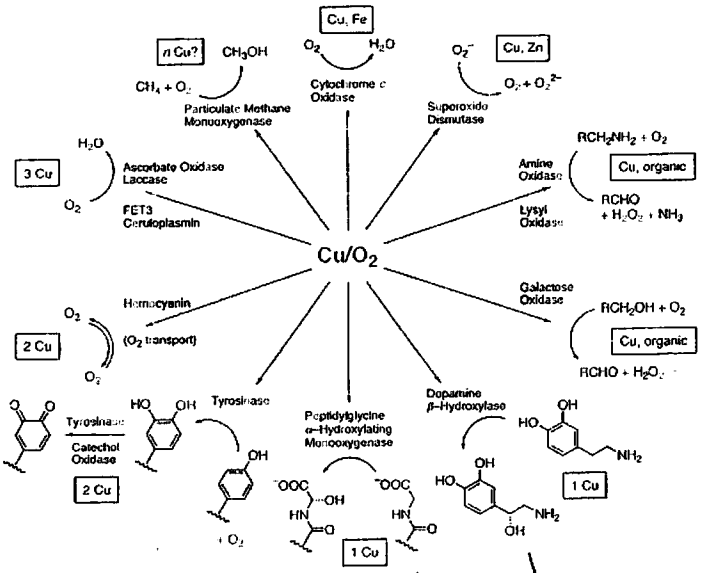


Figure 1. Selected Cu enzymes and proteins that activate O_2.[18]

Cu exists as mono- or multinuclear complex in enzymes.

Study of Mechanism has a potential to design a new oxidation catalyst.

} will be in discussion.

1.2 Methods of Studying Cu/O_2 complexes

Cu/O_2 complexes have been studied mainly by using synthetic ligand

$$Cu(I) \xrightarrow{O_2} Cu(II)O_2^{\cdot-} \xrightarrow{e^-} Cu(II)O_2^{2-} \xrightarrow{H^+} Cu(II)OOH$$

superoxo — peroxo — hydroperoxo

peroxo: thermodynamically more favorable than superoxo species.

- Mononuclear Cu(I) complexes easily self-assemble into binuclear species upon oxygenation.
  → Cu/O_2 2/1 complex is the most abundant of all Cu/O_2 species.

$$2Cu(I) \xrightarrow{O_2} [L Cu^{II}(O_2) Cu^{II} L]^{2+} \rightleftharpoons [L Cu^{III}_2(O)_2 L]^{2+}$$

	Cu_2^{II} – $\eta^2:\eta^2$ – μ-peroxo	Cu_2^{III} – bis-μ-oxo
(UV-vis λ(nm)	360, 520	300, 400)
[(IR (cm⁻¹)	740	600)

↳ other methods include resonance Raman spectroscopy, EPR, voltammetry, EXAFS, X-ray

- Mechanistic studies using Cu-O_2 adduct is only recent. (~10 years)
- Synthetic Ligands.

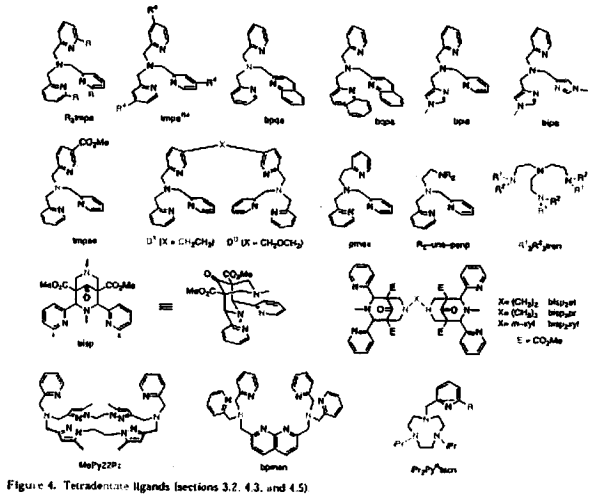


Figure 4. Tetradentate ligands (sections 3.2, 4.3, and 4.5)

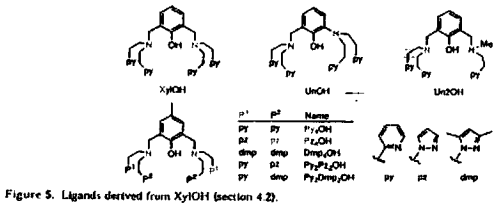


Figure 5. Ligands derived from XylOH (section 4.2).

Tetradentate.

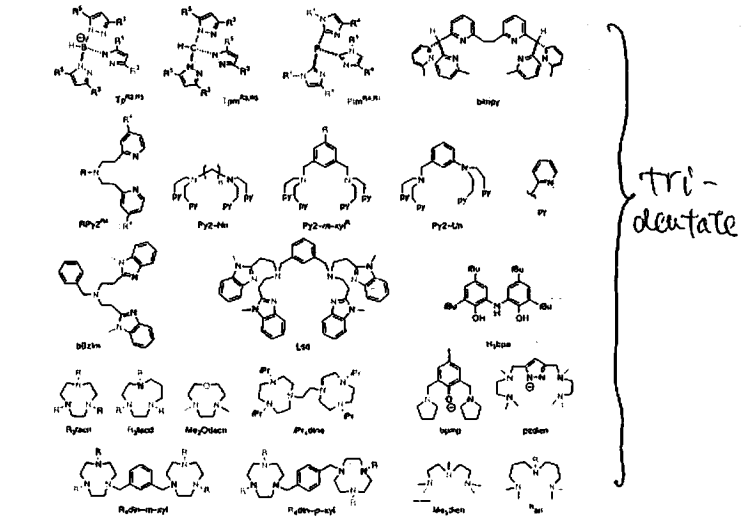


Figure 6. Tridentate ligands (sections 3.3.1 and 4.4–4.6).

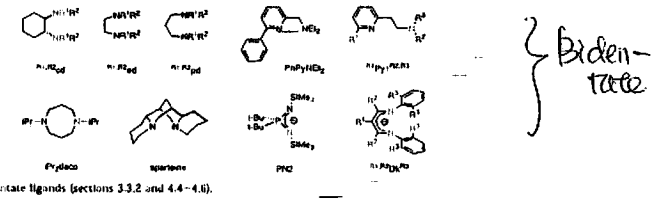


Figure 7. Bidentate ligands (sections 3.3.2 and 4.4–4.6).

Synthetic ligands are mostly N- or sometimes O- ligand.
(In enzymes, Cu are coordinated by N(histidine), S(methionine) or phenolate, H_2O and so on.)

Cu O=O

2. Reaction of Cu(I) with Oxygen
Cu/O₂ structure is largely influenced by ligands.

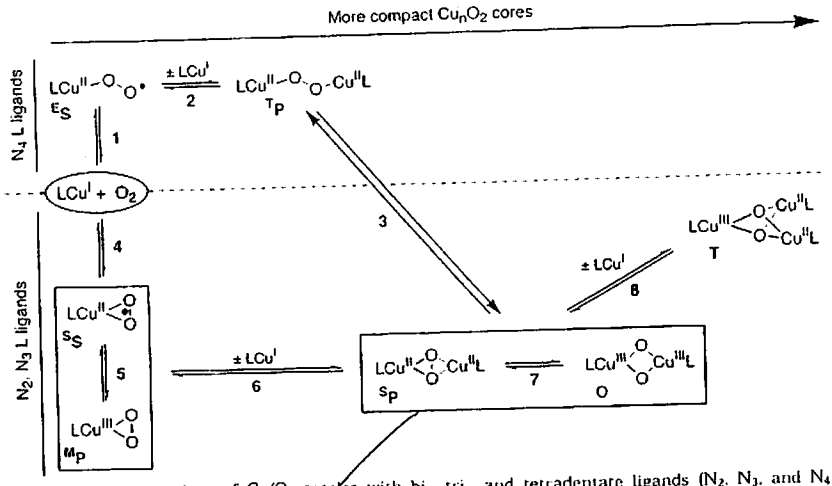
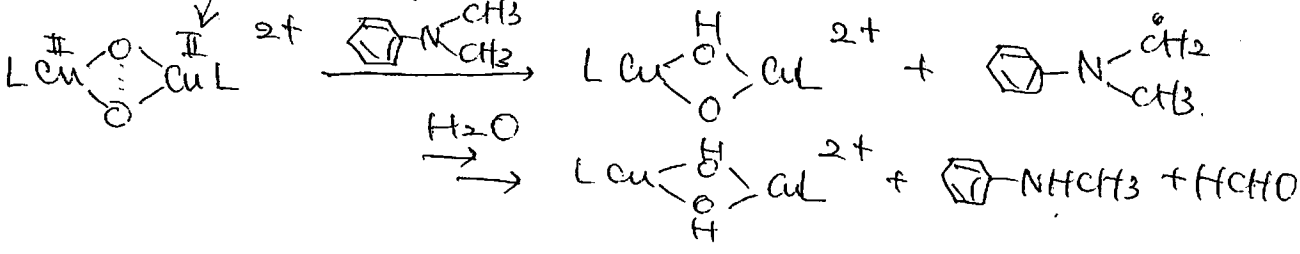


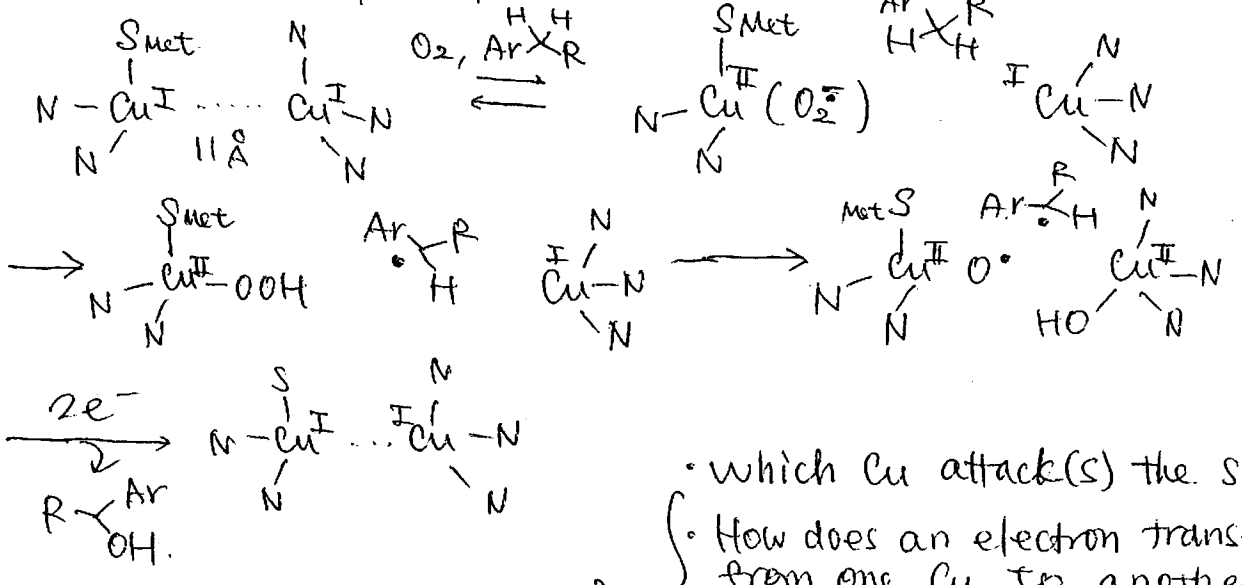
Figure 27. Formation reactions of Cu/O_2 species with bi-, tri-, and tetradentate ligands (N_2, N_3, and N_4 ligands, respectively).

3. Proposed oxidation mechanism of Cu/O_2 with substrates.
some selected examples.

ⓐ Cu/O_2 2/1 : N-dealkylation (P450)



ⓑ Cu/O_2 1/1 : hydroxylation (PHM, DBH)



What are still unclear today..?

- which Cu attack(s) the substrate
- How does an electron transfer (b) from one Cu to another? (b)
- H abstraction proceeds by concerted ($-H^{\bullet}$) or consecutive ($-e^{-}$, then $-H^{+}$) pathway?

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Date

Substrate Oxidation by Copper–Dioxygen Adducts: Mechanistic Considerations

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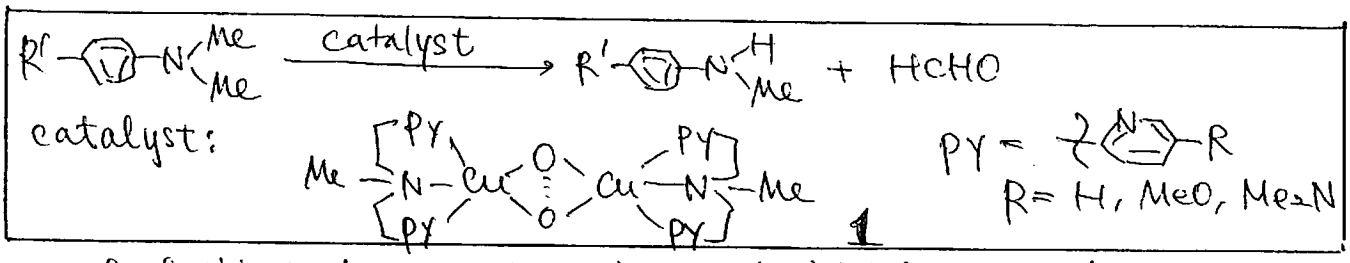
4. Mechanistic Studies.

Also preliminary studies : p. 12670-12671. JACS, 2003, 125,

Model reaction used in this study : N-dealkylation.

Why this reaction ?

- DMA (dimethylaniline) derivatives can be good probes for mechanism study.
- DMA has already been used in cytochrome-P450 chemistry, (ref. JACS, 2002, 124,).

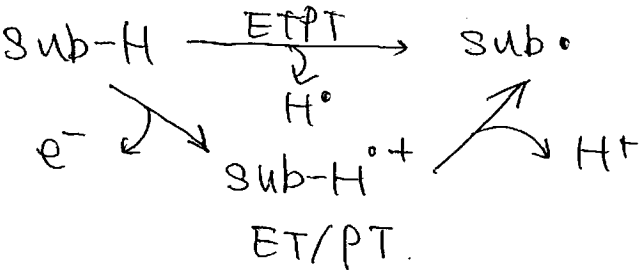


goal of this study : To investigate the initial steps of PCET reaction.
PCET = proton coupled electron transfer.

2 major points were clarified : ① ET/PT is dominant over ETPT.
② substrate coordination is necessary.

4.1. ET/PT or ETPT reaction ?

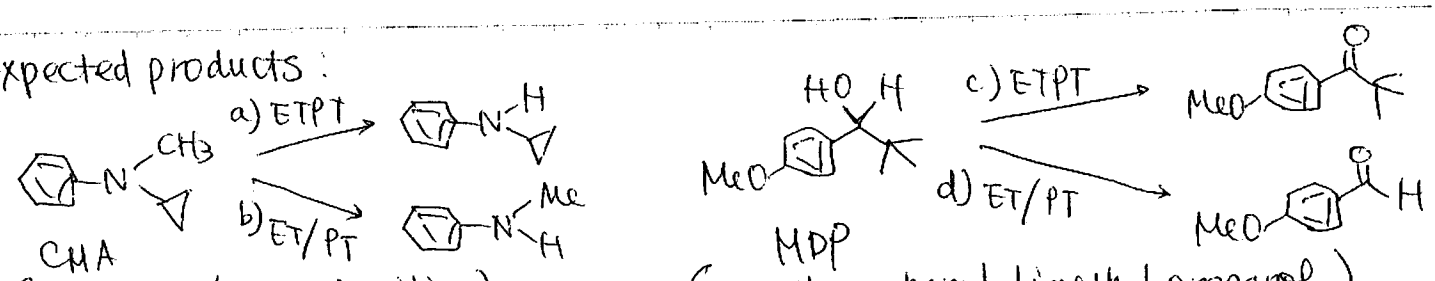
ET/PT : electron transfer (ET) and proton transfer (PT) in consecutive manner.
ETPT : ET and PT occurs in a concerted manner.



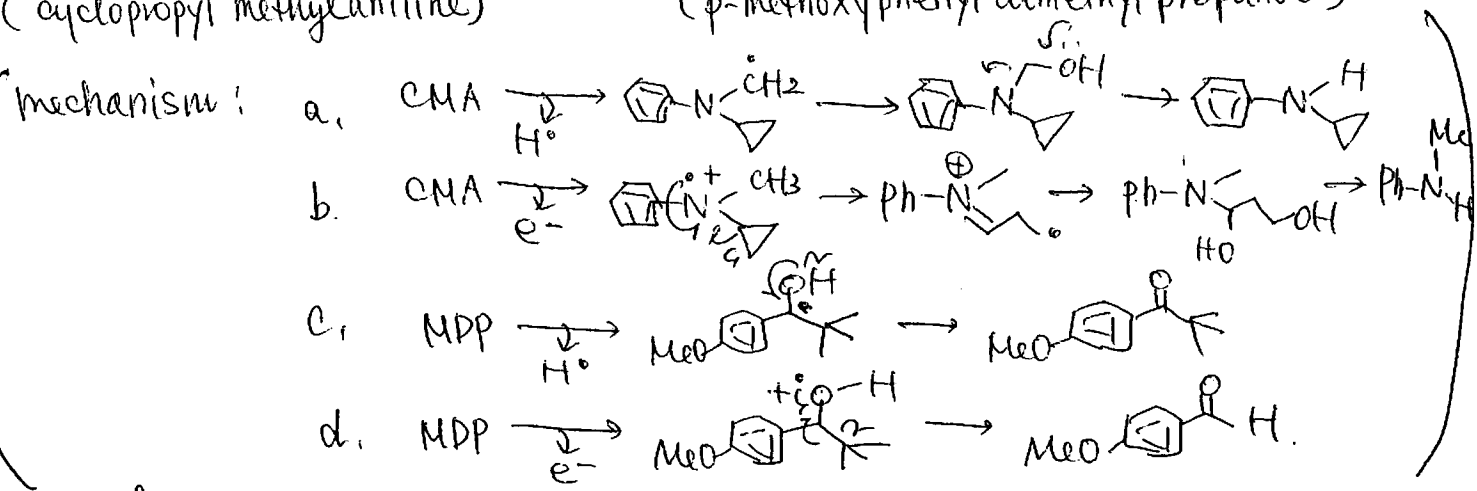
In JACS, 2003, 125, 12670.
KIE (kinetic isotope effect) was examined.
This study showed that ETPT and ET/PT are both plausible depending on the catalyst and substrate.

This time, more detailed studies using 2-probes, CMA and MDP.

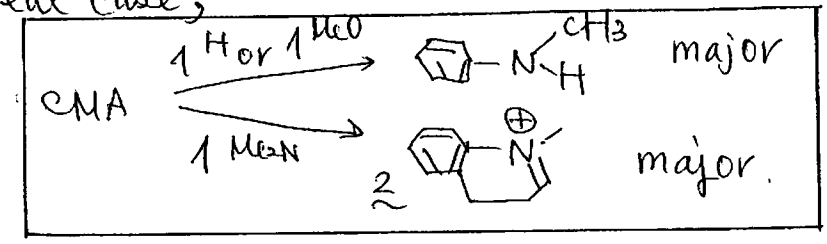
Expected products :



Mechanism :

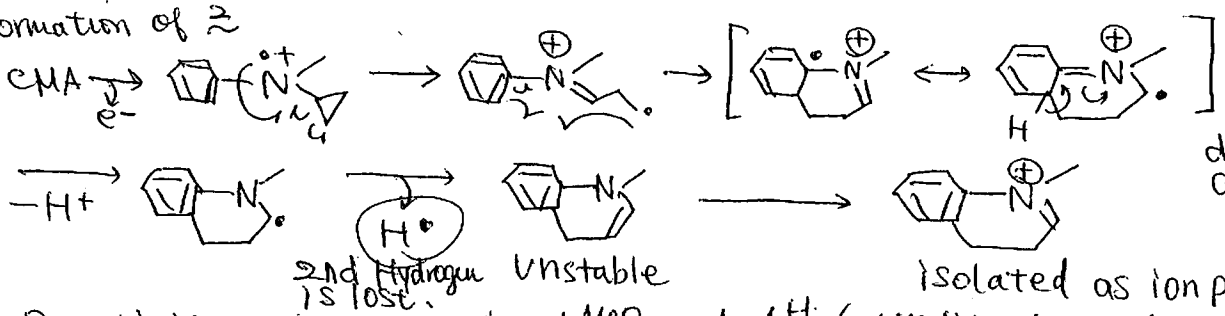


In real case,



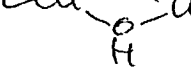
These results suggest that ET/PT pathway is dominant,

formation of 2

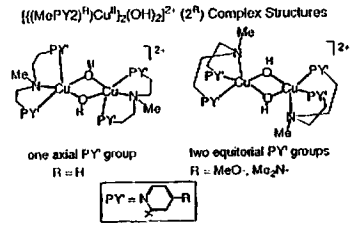


Reactivity : 1^{Me_2N} > 1^{MeO} and 1^{H} (1^{Me_2N} is the weakest SET oxidant!)

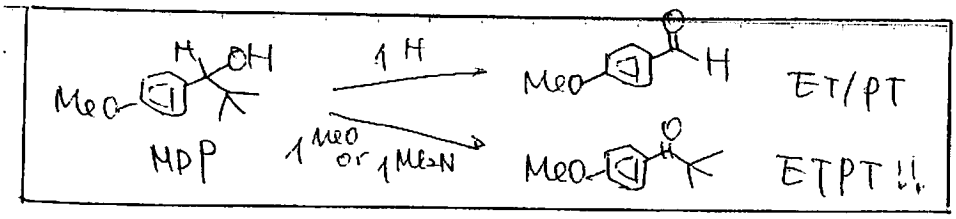
⇒ H° loss is faster than •OH capture.

* Factors that might influence the reactivity difference of 1^R.
  - Different ligand coordination environment
  - Differing amount of Cu^{III}_2-bis-μ-oxo isomer.
  - Stronger O–H bond strength in  that result from cat. 1^R.

Scheme 9. [{(MePY2)^{R}Cu^{II}}$_2$(OH)$_2$]$^{2+}$ (2^R) Complex Structures



In the case of MPP..



Why are the mechanism different depending on the substrate?
cf. BDE (bond dissociation enthalpy) of CHA and MPA.
are similar ; ~ 85 kcal/mol

* Oxidation potential : MPP > CHA (higher by 1.0V)

↓

ETPT may be the more accessible pathway with substrates possessing inaccessible oxidation potentials.

Then, why ET / PT is dominant with substrates with lower oxidation potential ?

" It appears that oxidations of substrates by one electron are aided by the thermodynamic driving force imparted by a proton transfer (PT) event. " (from the text).

$[Fe^{II}(phen)_2(phen\text{-}NO_2)](ClO_4)_2$

−80°C, 1R ↙ NO reaction.

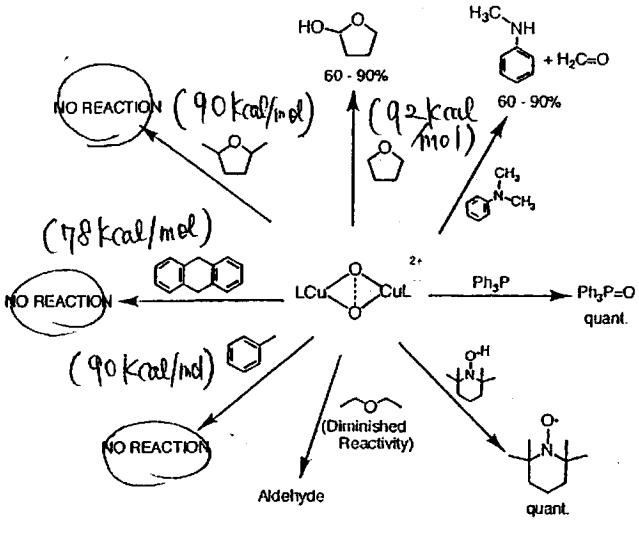
↘ −80°C, 1R, $NH_4^{\oplus}B(C_6F_5)_4^{\ominus}$ as proton source. → Fe^{III} !!

Conclusions : At low thermodynamic force, ET/PT occurs.
But when ET (one-electron oxidation) becomes uphill the ETPT pathway occurs.

↳ This phenomenon can be seen in other metal-oxo mediated oxidations.

7-2 Requirement for Substrate Coordination.

Scheme 4

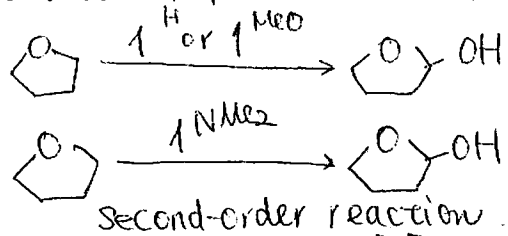


BDE is shown in parenthesis. (C-H bond)

↙

BDE cannot predict what substrate can be oxdized.

Insights into THF oxidation.



Second-order reaction.
$v = k[1^{NMe_2}][THF]$

1 eq. of CH_3CN (coordinative) affects the 2nd order rate constant dramatically.

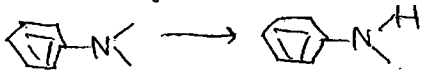
low activation enthalpy $\Delta H^{\ddagger} = 3.7$ kcal
negative activation entropy.
$\Delta S^{\ddagger} = -56$ cal/mol·K.

⇓

There should be a pre-equilibrium of THF and 1^{NMe_2} before oxidation occurs.

$1^{Me_2N} + THF \rightleftharpoons 1^{Me_2N} \cdot THF \rightarrow$ 

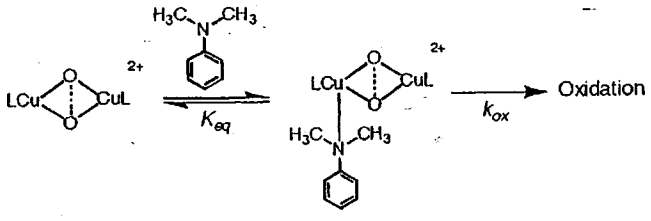
In the case of DMA oxidation:



Higher concentration (>20 mM) induces saturation behavior in reaction rate, especially at low temperatures (< −70°C).
(DMA binding is entropically disfavored. < −40 cal/mol·K.)

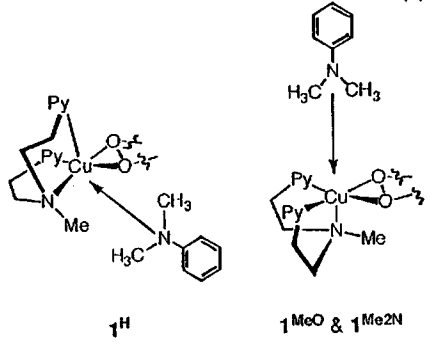
Conclusion:

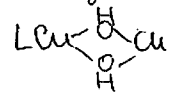
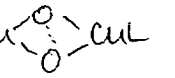
Scheme 6



Factors that would cause the reactivity difference between 1^H, 1^{MeO}/1^{Me_2N}

1. Difference in substrate approach to metal center.



Although direct evidence is lacking,  and  might have similar structures.

2. The ratio of peroxo : μ-oxo species.

1^H 90/10
1^{MeO} and 1^{Me_2N} 75/25

μ-oxo might be responsible for ETPT. cf. from MO calculations, it has been shown that peroxo species cannot promote ETPT.

Dioxygen Binds End-On to Mononuclear Copper in a Precatalytic Enzyme Complex

8

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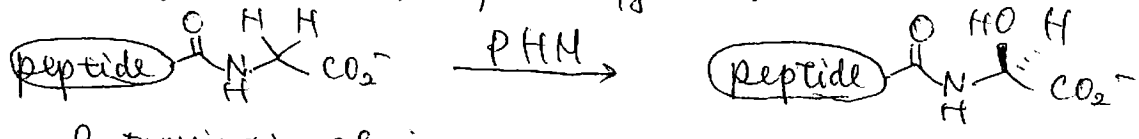
Science 2004 304, 864-867

5. First Structural Characterization of end-on Cu/O_2 (1/1) complex in enzymes.

PHM (peptidylglycine α-hydroxymonooxygenase)

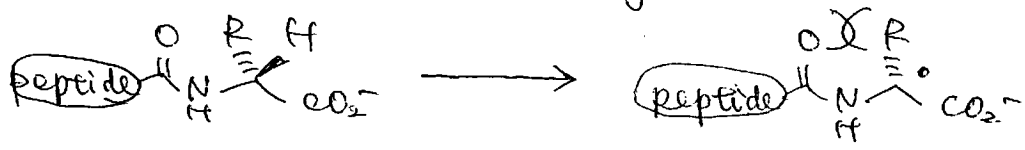


C-terminating glycine

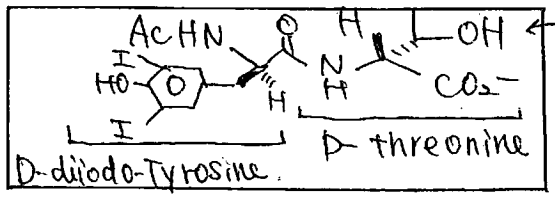
PHM (reduced form, Cu(I)) + peptide + O_2 → crystallization is difficult !!
It can rapidly promote catalysis

↓ to solve this problem..

Idea ✱ Use of ascorbate (to reduce Cu(II) and to stabilize Cu(I))
✱ Use of low reactive C-terminating amino acid.



Bulkier R group makes radical less stable due to the steric repulsion with amide carbonyl. (JACS, 2003, 125, 8119.)
↳ prevention of oxidation?



molecular modeling shows the hydrogen bonding with Tyr in PHM.

IYT peptide.

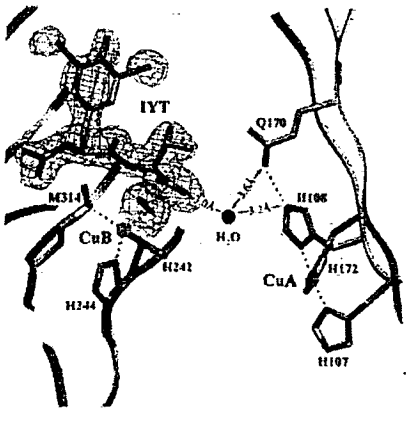


Fig. 2. The precatalytic complex of PHM with bound peptide and dioxygen. The 2Fo-Fc electron density (contoured at 1.5σ) is shown for dioxygen and the IYT peptide. Substrate and protein atoms are colored by atom type; iodine atoms are purple. The water molecule is represented by a red sphere and molecular oxygen by a red rod. Dotted lines indicate hydrogen bonds and bonds to the copper atoms (green spheres).

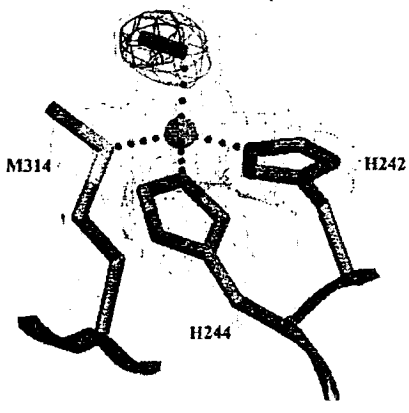


Fig. 3. The structure of the dioxygen binding site. Dioxygen (the red rod) is shown bound to Cu_B (the green sphere) in an end-on manner. Amino acid ligands to Cu_B are shown colored by atom type. A gray mesh represents 2Fo-Fc electron density contoured at 1.5σ. Simulated annealing difference omit maps that leave out either both oxygen atoms (red mesh) or the distal oxygen atom of dioxygen (blue mesh) are shown contoured at 8σ.

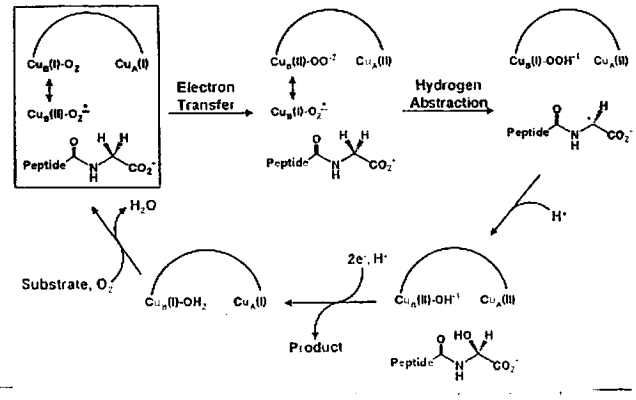
New Insights were given mechanistically from the structure

① Electron transfer path.

(CuB) – C terminus of peptide – H_2O – His 108 – (CuA)

$e^{\ominus}$

~ mechanism ~



Date

② • precatalytic PHM + IYT : Cu binds to O_2.
• oxidized PHM + IYT } Cu does not bind to O_2.
• precatalytic PHM only } (H_2O occupies the position)

⇓

Substrate might bind to Cu before O_2 binds.

This is favorable in nature because unwanted activation of O_2 does not occur.

6. Conclusions + Future

- Thermodynamic instability of Cu/O_2 adducts is typical.
  negative entropy ⇒ controllable by ligand ?
  favorable enthalpy

  * Critically important kinetic and thermodynamic information has been obtained using stopped-flow UV-vis spectroscopy.

    ‖

    Time-course of UV-vis absorption at low temp. can be collected. kinetics for fast reaction can be analysed.
  * Cu/O_2 adducts stable at room temperature is rare.

- Mechanistic studies of mono or tri (or more) nuclear Cu/O_2 complexes.